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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,765	10/02/2003	George N, Serbedzija	018852-000511US	1627

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/678,765	SERBEDZIJA ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/08/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment dated 03/15/2006 has been entered. Claims 1-30 have been cancelled. Claims 31-38 are pending and under consideration in the instant office action.

Specification

The disclosure is objected to because of the following informalities: The priority information at the first line of the specification should be updated to indicate that USSN 09/645,432 has been allowed as USPN 6,656,449 and USSN 09/255,397 has been allowed as USPN 6,299,858.

Appropriate correction is required.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: The Brief Description of the Drawings at page 10, line 28 refers to Figures 17A and B but does not refer to Figure 17C. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not

accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: Support for screening an agent for toxicity in a teleost comprising detecting a change in expression of a protein or mRNA is not supported by either of US provisional applications 60/075,783, filed 02/23/1998 or 60/100,950, filed 09/18/1998. '783 refers generically to screening compounds for an activity, specifically refers to angiogenesis and contemplates screening agents for toxicity at page 5, paragraph 6 by means of observing an increase in normal blood vessel formation. The specification of '783 does not teach generic assessment of toxicity of a compound by assaying protein or mRNA expression. '950 appears to be directed to screening for agents involved in modulating cell death in a manner that would be therapeutic and does not mention assessment of toxicity of a compound by assaying protein or mRNA expression. Therefore, priority to these documents for the instantly pending claims is denied. The effective filing date granted for the claims is 02/22/1999 based on support in US Application 09/255,397.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

Claims 31,33 and 35-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening an agent for toxic activity comprising administering an agent to a teleost in vivo, processing said embryo in vitro in a manner to detect expression of a protein or mRNA in a specific organ or tissue, and quantifying mRNA or protein expression, wherein a change in said mRNA or protein expression in comparison to a control teleost embryo not administered the agent is indicative of toxic activity of the agent, does not reasonably provide enablement for the claimed method wherein the expression of said mRNA or protein is detected in vivo or for the claimed method without a control for comparison. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by

weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims appear to be lacking methodology, rendering the claims overly broad. The claims encompass in vivo monitoring of mRNA or protein levels in vivo over a period of time wherein a change in mRNA or protein expression is indicative of toxicity. The specification has taught measuring toxicity of an agent by assessing the toxic activity of an agent relative to a contemporaneous and/or historical control to which the agent has not been administered (page 75, lines 6-9). The specification has taught means of measuring expression that requires sacrifice of the teleost. The specification does not teach in vivo measurement of gene expression as encompassed by the claims.

The claims fail to recite any type of experimental control for comparison and the specification does not provide any guidance as to how to carry out the method without a comparison to a baseline control. As set forth above, the specification does not teach in vivo assays of mRNA or protein expression and therefore, the comparison cannot be made over time in the same teleost. Therefore, some other comparison is necessary to constitute a "change in expression" as claimed.

Claim 31 recites that "a response" in the teleost is indicative of toxic activity. The specification defines "response" as a change in gene expression (page 76, lines 25-29). However, to determine a "change", one must have a baseline from which to characterize a change. For example, the specification does not indicate any concrete standards to which a particular mRNA or protein level in a treated fish should be compared. Therefore, because the specification teaches comparing a treated teleost to an untreated control, claims should be limited as such.

Enablement

Claims 32 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 32 and 34 are not enabled by the specification because the specification fails to teach how to monitor protein or mRNA activity in a single embryo over time (page 80, line 26; page 81, line 16; page 82, line 12). This limitation, "response...is detected over time" in claim 32 can be interpreted to mean multiple responses of a single teleost, detected over a time period. The specification teaches assays requiring fixation of the embryos. Other assays required lysis of the embryos (page 82, line 25). Doing so precludes monitoring at a second time point. Thus, given the assays in the specification that require fixation or destruction of the embryo to monitor protein or mRNA at a first time point, one of skill in the art would not know how to carry out an assay at a subsequent time point.

Claims 32 and 34 are further not enabled for the reasons set forth above in the scope of enablement rejection. Claims 32 and 34 depend from claim 31, which lacks enable for the full breadth of the claim as written.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 is unclear because it refers to a "change in expression" without setting forth a basis for determining the change. Claims 32-38 depend from claim 31.

Claim 31 is unclear because "a response" in line 5 is not definitively linked to "a change in expression" at lines 2-3. It is not clear whether "a response" is referring to the "change in expression" or if it includes other potential responses such as changes in morphology. Claims 32-38 depend from claim 31.

Claim 31 recites the limitation "the at least one tissue or organ" in lines 4-5. There is insufficient antecedent basis for this limitation in the claim. Claims 32-38 depend form claim 31.

Claim 32 is unclear because of the use of the terminology "detected over time". It is unclear if the claim is meant to include multiple sampling of a particular teleost over a period of time or that the toxic activity is not detectable until a period of time has passed.

Claim 34 is unclear because it is not clear whether the toxic activity is measured at intervals over a period of time or if the toxic activity occurs at intervals over a period of time.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Mizell [1997, IDS].

As set forth above, priority to US provisional applications 60/075,783 and 60/100,950 for the instantly claimed subjected matter has been denied. The effective filing date is 02/22/1999.

Claim 31 is drawn to a method of screening an agent for toxic activity in vivo comprising administering an agent to a teleost and detecting a change in expression of a protein in a specific organ or tissue of the teleost, a response in the teleost indicating toxic activity in the tissue. Claim 32 requires that toxic activity be detected over time. Claim 33 requires that the response be detected in at least two tissues. Claim 34 requires that the response is over time at predetermined intervals. Claim 35 requires simultaneous testing of at least 2 teleosts.

Mizell taught a method for screening an agent for toxic activity in both zebrafish and medaka, which are teleosts. Mizell taught administering the agent (TCDD, toluene, benzene) to multiple (claim 35) dechorinated zebrafish embryos and detecting toxic effects by monitoring CYP1A activity (see page 416, last paragraph-page 416, paragraph 2, page 419, col. 2, paragraph 2; see Table 5, line 2 at page 96 of the specification). Early activation of CYP1A was shown as an indicator of TCDD toxicity. Multiple embryos were assayed at a time (page 421, col. 2,

paragraph 4), meeting the limitations of claim 35. Mizell taught that toxic activity is detected after a 30 minute exposure to TCDD (page 415, col. 2, paragraph 2), which constitutes detecting toxicity over time at a predetermined interval as required by claims 32 and 34. Mizzel observed changes in heart formation as well as Cyp1A activity in both the gut and liver, fulfilling the limitations of claim 33.

Therefore, Mizell taught the limitations of claims 31-35.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mizzel (1997) as applied to claims 31-35 above, and further in view of Terse [1993, **Toxicon**, 31:913-919].

As set forth above, Mizell taught a method for screening an agent for toxic activity in teleosts. Mizell taught administering toxins to zebrafish embryos and detecting toxic effects by monitoring CYP1A activity as an indicator of toxicity. Mizell taught placing each embryo in a single droplet of medium in a single large Petri dish (page 421, col 2, paragraph 4). Mizell did not teach placing each embryo in a well of a multi-well plate (claim 36) wherein the volume of the wells is 300 microliters or less per well (claim 37).

However, Terse et al. taught screening the toxic activity of various mycotoxin agents using 96-well multi-well plates. As evidenced by the specification, standard 96-well plates have a volume of 300 microliters (see page 88, lines 27-29).

It would have been obvious to one of skill in the art at the time of filing to combine the teachings of Mizell in screening agents for toxicity using teleosts with the teachings of Terse *et al*,. to carry out an in vivo toxin screen using 96-well microtiter plates. One would have been motivated to combine these teachings because multiwell plates provide a more convenient means of separating samples without cross-contamination or loss of sample. Terse *et al.* did not specify a volume in which to place the sample in the well, however, in light of the teachings of Mizell using 250µl droplets and the upper volume limit of the wells being 300 µl, one of skill in the art would have been motivated to use a smaller volume of liquid in the multi-well plate to avoid spill over from one well to another and to conserve and to work with smaller amounts of potential toxin. It was obvious to one of skill in the art by looking a teleost embryo, that 200 µl would be more than sufficient to envelope the entire teleost.

One would have a reasonable expectation of success in carrying out a screen as taught by Mizzel using 96-well plates as taught by Terse *et al.* because it was standard in the art to carry out screens in 96-well plates and the multi-well plates are made of a material similar to Petri-dishes and serve the same purpose, only with an added benefit.

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

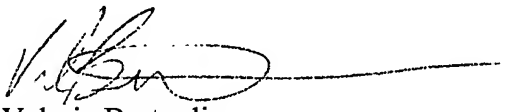
Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Valarie Bertoglio
Examiner
Art Unit 1632